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ART UNIT	**PAPER NUMBER**
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/697,419	PATTERSON ET AL.	
	Examiner	Art Unit	
	Iqbal H. Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,7-12,14,27 and 31-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *4, 14 and 39* is/are allowed.

6)☒ Claim(s) *1-2, 7-12, 27, 31-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-2, 4, 7-12, 14, 27, 31-33 and 34-39 are currently pending in the instant application.

Applicant's amendment of claims 1 and 9, canceling claims 15-26 and 29, and adding new claims 34-39 filed on January 2, 2008 is acknowledged. Claims 3, 5-6, 13, 28, and 30 remain cancelled.

Claims 1-2, 4, 7-12, 14, 27 and 31-39 are under consideration and are being examined herein.

Applicants' amendments and arguments filed on January 2, 2008, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Withdrawn Claim Rejections - 35 U.S.C. § 112 (2nd)

Previous rejection of Claims 1-2, 7-12 and 31-33 under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicants amendment of claim 1.

Maintained Claim Rejections - 35 U.S.C. § 112 (1st)

Previous rejection of Claims 9-10, 12 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated host cell transformed with the recited nucleic acids does not reasonably provide enablement for any cell within a multicellular animal which have been transformed with the recited nucleic acids is maintained. The rejection has been discussed at length in the previous Office action. The rejection is maintained for the following reasons.

Claims 9-10, 12 and 14 are so broad as to encompass any cell transformed with specific nucleic acids, including cell in *in vitro* culture as well as cells within any multicellular organism. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of host cell broadly encompassed by the claims. While methods for transforming cell *in vitro* are well known in the art, methods for successfully transforming cells within complex multicellular organisms are not routine and are highly unpredictable. Furthermore, methods for producing a successfully transformed cell within one multicellular organism are unlikely to be applicable to transformation of other types of multicellular organisms as multicellular organisms vary widely. However, in this case the disclosure is limited to only host cell in vitro.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including the use of any cell within a multicellular organism for the production of polypeptide. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, expression of genes in a particular host cell having the desired biological characteristics is

unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is suggested that applicants limit the claims to "An isolated host cell".

Applicants argue that the §101 rejection based on non-statutory subject matter is incorrect because the claimed subject matter is directed to a "cell" not a "human being" and it is not the law that something capable of being introduced into a human being (such as a non-naturally occurring genetically modified cell) is non-statutory subject matter. Applicants also argue that if the law were otherwise, every patent covering anything that is capable of introduction into a human being (e.g., an implantable medical device, a drug, a contrast agent, a nutritional supplement, a hair-coloring dye, an ink for tattoos, or a suppository) would be invalid.

This is not found persuasive because the rejection is not a §101 but lack of enablement under §112 1st, i.e. an isolated host cell transformed with recited nucleic acid molecule is enabled but any cell which includes naturally occurring cell or a cell of multicellular organism transformed with recited nucleic acid is not enabled. claims still read on any cell including naturally occurring or a cell of multicellular organism, which includes human being comprising recited nucleic acid molecule, and the claims do not recite "something capable of being introduced into a human being" or "non-naturally genetically modified cell" as argued by the applicants. It is not "something capable of introducing into a human being" rather the cells within the organism itself that applicants are claiming. Cells within an organism are not the same as cells in culture or cells introduced by "ex-vivo" methods (both of which are isolated cells).

Applicants also argue that "claims themselves are directed to a cell- not a genetically modified animal". This is not found persuasive because "a cell' transformed with recited nucleic acid implies any cell as written, which includes naturally occurring cell or a cell within an organism, i.e. a cultured transformed cell is different than a cell within an organism. Thus, the claim reads on a genus of different transformed cells; the full scope of which is not enabled. The rejection is not drawn to lack of enablement of a genetically modified animal (as this is not claimed) but to lack of enablement of how to make transformed cells that are within a multicellular animal as these cells are a portion of the scope of what is claimed.

Applicants further argue that "as set out in the Spectra-Physics --- not every single possible method of making every possible ---- needs to be explicitly taught in order to meet the enablement requirement. This is true but "a cell" as claimed is not commensurate to the full scope of the claims, i.e. claims are enabled for an isolated cell transformed with recited nucleic acid but not any cell. Applicants were never required to describe every embodiment but only to have enabled the full scope of what the claim. Since, the claim is all transformed cells; they need to reasonably teach how to make any such cell not just those that are isolated.

Furthermore, applicants argue that they cannot understand the reasoning that claims directed to a cell are non-statutory subject matter because they might be placed in a human subject, whereas the claims directed to a nucleic acid (which were not rejected in this basis; e.g. claim 1), which also might be placed in a human being, are statutory subject matter. This is not found persuasive because the issue is not a non-statutory subject matter rejection rather enablement issues. An isolated nucleic acid (which is man made" is enabled if it is introduced in

an isolated host cell including mammalian cells but any transformed cell, which can be a transformed naturally occurring or a transformed cell of a multicellular organism, is not enabled.

In addition, applicants argue that why "a cell" is not enabled in the instant application, although a claim in US Patent (5,874,394), which recites "A recombinant host cell", which is enabled. The Examiner examines the case based on the fact of the instant application, cannot reexamine an issued patent examined by another examiner. However, the claimed cell of the US Patent is "A recombinant host cell", which is completely different than the claimed cell of the instant application, i.e. "A cell".

In support of the Examiners argument, applicants' new claims 35-39 recite "an isolated host cell" comprising recited nucleic acid, which are enabled and claims do not read on any naturally occurring cell or a cell within a multicellular organism.

Therefore, the rejection of claims 9-10, 12 and 14 are maintained.

Maintained Claim Rejections - 35 USC § 103

Previous rejection of Claims 1-2, 7-12, and 27, are rejected under 35 U.S.C. 103(a) as being obvious over Szittner et al. (J Biol Chem. 1990 Sep 25; 265(27): 16581-7, see IDS), Mao et al. (Zhonghua Zhong Liu Za Zhi, 2001 Sep; 23(5): 359-62, article in Chinese) in view of Zolotukhin et al. (US Patent 5,874,304, publication 2/23/1999) is maintained and claims 34-38 are included in this rejection. Instant claims are directed to a codon optimized nucleic acid comprising a gene encoding LuxA protein from Photorhabdus luminescens, a vector comprising

said gene having regulatory sequence, a transformed host cell and a kit comprising said nucleic acid molecule for analyzing gene expression.

Applicants argue that the foregoing rejections are almost identical to the § 103 rejections presented in the office action mailed June 20, 2006 and in the office action mailed November 30, 2006, the examiner stated that this rejection was withdrawn in view of applicants' amendments and argument. Applicants also argue that the presently pending claims are all patentable over the foregoing combination for the same reasons that successfully overcame the previous §103 rejections (see applicants' September 19, 2006 amendment). Accordingly, applicants believe that these rejections are in error and requests their withdrawal or further clarification of why the withdrawn rejections were re-instated. The Examiner acknowledges that there was an error in withdrawing the rejection but after careful analysis, the Examiner reinstated the rejection based on the following reasons.

Applicants' main argument in the remarks of 9/19/2006 was that the combination of Szittner et al. Mao et al. and Zolotukhin et al. Greer et al. and Lowe et al. fails to provide any motivation or suggestion to make the claimed invention because none disclose any reason why it would be advantageous to codon optimize LuxA. This is not found persuasive because Zolotukhin et al. shows a clear motivation that codon optimization of a gene encoding protein such as GFP; increase the production of said protein in a specific host cell which is corresponding to specific codon optimization. Indeed, codon optimization of a protein is also well known in the art, wherein codon optimization depends on a particular host specific, not depends on the desired protein, which to be overexpressed in increased amount. Since, Szittner et

al. teach LuxA (luciferase) gene from Xenorhabdus (same as Photorhabdus) luminescens, which is 70% identical to SEQ ID NO: 1 of the instant application, wherein the source of LuxA gene of the instant application also from Photorhabdus luminescens and Mao et al. teach the expression of fused LuxAB gene of bacterial luciferase as a reporter gene in mammalian liver carcinoma cells, wherein Zolotukhin et al. teach a humanized green fluorescent protein (GFP) genes and method of use for high-level expression in mammalian cells especially those of human origin by using base substitution in codons in order to change the codon usage for efficient expression in mammalian cells.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to combine the teachings of Szittner et al., Mao et al. and Zolotukhin et al. to codon-optimize LuxA gene of Szittner et al. including substituting the leucine codon CTG instead of other leucine codons as disclosed by Zolotukhin in order to increased expression in mammalian cell in order to development of a mammalian bioluminescence bioreporter system to be used in medical research and diagnostics applications. One of ordinary skill in the art would have been motivated to use codon-optimized LuxA gene for mammalian cells in order to maximum expression in that mammalian cells for the efficient and stable enzyme activity in terms of luminescence to be used in medical research and diagnostics applications. As such the Examiner has responded to applicants previous arguments and explained why they are deemed insufficient to overcome the rejection.

Applicants also argue (current remarks) that the Lux system of the present application is significantly different from the GFP system described in the Zolotukhin et al. patent. Unlike monomeric GFP, the Lux enzyme is a heterodimeric protein that needs both Lux A and Lux B to

produce light, and because of the required association with Lux B, before the experiments described in the application, it could not reasonably have been predicted that codon-optimizing LuxA would produce more light than the wild type version. This is not found persuasive because codon optimization of a cDNA for higher expression of encoding protein is well known in the art and although the GFP and LuxA are different but the purpose of codon optimization is the same i.e. expression of protein in higher amounts in a particular host cell. As Lux enzyme is a heterodimeric protein, therefore, same codon optimization to express both proteins is required for activity, which can be done as taught by Zolotukhin et al. As argued, Zolotukhin et al. which was used as one of the reference in this 103 rejection, clearly show that codon optimization indeed results in higher expression of a protein in a particular host irrespective of what kind of protein codon is optimized.

As stated previously, Szittner et al. teach LuxA (luciferase) gene from Xenorhabdus (same as Photorhabdus) luminescens, which is 70% identical to SEQ ID NO: 1 of the instant application, wherein the source of LuxA gene also from Photorhabdus luminescens. Szittner et al. also teach the cloning of Lux genes required for expression of luminescence, complete nucleotide sequences of the LuxA gene coding for the alpha subunit of luciferase. Szittner et al. further teach that the luciferase from X. luminescens have a remarkably high thermal stability being stable at 45 degrees C (t 1/2 greater than 3 h) and suggested that the X. luminescens Lux system might be used for application in coupled luminescent assays and expression of Lux genes in eukaryotic systems at higher temperatures. Szittner et al. do not teach the use of codon-optimized or codon usage of LuxA gene for maximum expression with stability in eukaryotic or

mammalian cells.

Mao et al. teach the expression of fused LuxAB gene of bacterial luciferase as a reporter gene in mammalian liver carcinoma cells. Mao et al. also teach cloning bacterial luciferase LuxA and B gene in the mammalian expression vector pcDNA3, wherein the promoter and enhancer is from cytomegalovirus (CMV) and transfected into BEL7402 cell and determined the luciferase activity with standard assay method. Mao et al. do not teach codon-optimized LuxA gene.

Zolotukhin et al. teach a humanized green fluorescent protein (GFP) genes and method of use. Zolotukhin et al. also teach synthetic and humanized versions of GFP genes adapted for high-level expression in mammalian cells especially those of human origin by using base substitution in codons in order to change the codon usage for efficient expression in mammalian cells. Zolotukhin et al. also teach increase number of CTG or CTC leucine encoding codons, increase number of TTC for phenylalanine encoding codons and increase number of ATC isoleucine encoding codons of GFP amino acid sequence. Zolotukhin et al. also teach cloning the modified gene in expression vector and expressing in mammalian cells at higher efficiency.

It would have been obvious to one of ordinary skill in the art at the time of the invention was made to combine the teachings of Szittner et al., Mao et al. and Zolotukhin et al. to codon-optimize luciferase gene of Szittner et al. including substituting the leucine codon CTG instead of other leucine codons as disclosed by Zolotukhin in order to optimum expression of said gene in mammalian cell and to clone the codon-optimized gene in mammalian expression vector under the regulation of promoter/enhancer as disclosed by Mao et al. to use the codon-optimized

Lux system in the development a mammalian bioluminescence bioreporter system as a kit to be used in medical research and diagnostics applications.

One of ordinary skill in the art would have been motivated to use codon-optimized LuxA gene for mammalian cells in order to maximum expression of said gene in that mammalian cells for the efficient and stable enzyme activity in terms of luminescence to be used in medical research and diagnostics applications.

One of ordinary skill in the art would have a reasonable expectation of success because use of codon-optimized gene for over-expression with higher stability in a mammalian cell is customary and widely used in the art.

Therefore, the rejection is maintained.

Previous rejection Claims 31-32 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Szittner et al. (J Biol Chem. 1990 Sep 25; 265(27): 16581-7, see IDS), Mao et al. (Zhonghua Zhong Liu Za Zhi, 2001 Sep; 23(5): 359-62, article in Chinese) in view of Zolotukhin et al. (US Patent 5,874,304, publication 2/23/1999) as applied to claims 1-2, 7-12, and 27 above, and further in view of Greer et al. (Luminescence. 2002 Jan-Feb; 17(1): 43-74, Review) and Lowe et al. (US Patent 6,132,983) is also maintained for the similar reason as discussed above as applicants did not give separate arguments for this rejection but rather combined the arguments with the rejection of claims 1-2, 7-12, and 27.

A stated previously, Szittner et al., Mao et al., and Zolotukhin et al. teach LuxA (luciferase) gene from Xenorhabdus, codon-optimized or codon usage of LuxA gene for maximum expression in mammalian cells as discussed above. Szittner et al., Mao et al., and

Zolotukhin et al. do not teach the use of codon-optimized LuxA gene for making a kit for analyzing gene expression or using IRES promoter for expression.

Greer et al. teach LuxA gene from Photorhabdus luminescens and marine Vibrio harveyi bacteria, as well as eukaryotic luciferase luc and ruc genes from firefly species (Photinus) and the sea pansy (Renilla reniformis), respectively, that emit light in the presence of oxygen and a substrate (luciferin), cloning in a vector having selectable marker, expression using different promoter and enhancer including IRES in cell cultures, individual cells, whole organisms, and transgenic organisms. Greer et al. also teach humanized luciferase i.e. codon-optimized for expressing human cells. Greer et al. do not teach a kit for testing gene expression in cultured cells.

Lowe et al. disclose a luciferase gene encoding protein from Photinus species, cloning in expression vectors having restriction site, promoter and enhancer, host cells. Lowe further discloses a test kit and reagents for carrying out luminescence assay by using luciferase protein to determine the gene expression.

It would have been obvious to one of ordinary skill in the art at the time of the invention was made to combine the teachings of Szittner et al., Zolotukhin et al. Greer et al and Lowe et al. to develop a test kit for carrying out luminescence assay to determine the gene expression as disclosed by Lowe et al. by using LuxA gene of Szittner et al. by optimizing the codon usage as taught by Zolotukhin et al. by using vectors having restriction sites, promoter/enhancer including IRES as well as selectable marker to determine a gene expression in a sample.

One of ordinary skill in the art would have been motivated to develop a testing kit using codon-optimized LuxA gene for determining gene expression in mammalian cell sample to be used in medical research and diagnostics applications.

One of ordinary skill in the art would have a reasonable expectation of success because making a testing kit by using codon-optimized luciferase to determine the gene expression is customary and widely used in the art.

Therefore, the above references render the claims 31-33 prima *facie* obvious to one of ordinary skill in the art.

Conclusion

Status of the claims:

Claims 1-2, 4, 7-12, 14, 27 and 31-39 are pending.

Claims 1-2, 7-12, 27, and 31-38 are rejected.

Claim 4, 14 and 39 are allowed.

Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution. **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R.

§ 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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